REMARKS

Applicant respectfully requests reconsideration. Claims 1-29 are pending in the application. Claims 21 and 22 have been amended. Claims 3-4, 6, 9-11, 14-16, 19, and 23-25 are withdrawn. No new matter has been added.

Applicants expressly reserve the right to prosecute claims of similar or differing scope. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Office will be addressed below in the order they appear in the prior Office Action.

Rejection based on 35 U.S.C. § 103(a). Claims 1-2, 5, 7-8, 11, 13, 17-18, 20-21, and 26-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 7,060,299 (hereinafter, "Alavattam"), in view of Norris et al., J. Apply. Poly. Sci., 63: 1481-1492 (1997) (hereinafter, "Norris") and in view of U.S. Patent No. 7,157,426 (hereinafter, "Quay").

Independent claim 1 recites a surface-altering agent disposed on the surface of a core that enhances the average rate at which the particles or a fraction of the particles move in mucus by at least five-fold compared to the same particles except without a surface-altering agent disposed on the surface. Independent claim 20 is similar to claim 1 except it recites a bioactive agent disposed on the surface of the particle which enhances the rate of transport in mucus. The Patent Office is correct in stating that Alavattam does not specifically teach the enhancement of the average rate at which the particles or a fraction of the particles move in mucus by at least five-fold. However, the Patent Office states on page 6 of the Office Action that Norris teaches appropriate formulas for enhancing the rate of particle transport and that these formulas could be applied to the teachings of Alavattam, but without any reasoning to believe this would be the case. Applicant respectfully disagrees with the Patent Office's assumption.

Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. KSR International Co. v. Teleflex Inc., 550 U.S. 398, (2007). The burden is on the Patent Office to show that one of ordinary skill in

the art can make the claimed invention with a reasonable expectation of success. Specifically, the Supreme Court, in KSR International Co. v. Teleflex Inc., 550 U.S. 398, (2007), stated, based on the cited art, that "a rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art." Thus, the burden is on the Patent Office to establish a prima facie case of obviousness which includes a reasonable expectation of success, i.e., that the combined references teach or suggest a predictable outcome. Applicant believes that the Patent Office has not met this burden.

The formulas disclosed in Norris merely teach one how to calculate values of translocation permeability, the aqueous diffusion coefficient, and permeability, respectively, but do not give any indication of *how* to enhance the rate of particle transport in mucus. For instance, FIG. 8 of Norris shows different values of translocation permeability for microspheres functionalized with different functional groups (e.g., amidine, carboxyl, carboxylate-modified, and sulfate). As these data were obtained for particles simply having different surface functional groups, these data give no indication of what types of surface-altering agents (e.g., proteins, surfactants, sugars or sugar derivatives, nucleic acids, polymers, and other entities described in the instant specification) could be used to enhance the average rate at which the particles move in mucus as claimed. Notably, functional groups are quite different from surface-altering agents and would be expected to have different effects on the rate of transport of particles through mucus.

The Patent Office further suggests that since Norris performed studies of the effective size, surface charge, and hydrophobicity of particles in relation to the rate of particle transport, that these studies could somehow be applied to the teachings of Alavattam. First, Alavattam does not teach or suggest the transport of particles in mucus at all; as such, the particles are not tailored to have an increased rate of transport in mucus. Second, the studies provided by Norris on particle size, surface charge, and hydrophobicity appear to be inconclusive and do not guide one of ordinary skill in the art to determine how to enhance the rate of particle transport in mucus by using surface-altering agents, e.g., as measured by translocation permeability (P_T). For example, page 1491, left column of Norris states that, "while it appears that there is a relationship between the surface

ionization and P_T, further study is required to quantify these effects. The results shown in Figure 11 indicate that zeta-potential may not be a significant factor in determining the P_T of PS MS." [Emphasis added.] Norris also states on page 1491 that "current results (Figure 10) also suggest that an optimal hydrophobic-hydrophilic balance may be needed to facilitate the diffusion of MS through mucin." Norris does not explain what this optimal hydrophobic-hydrophilic balance may be nor the factors that would affect this balance. For at least these reasons, one of ordinary skill in the art at the time of filing, combining the teachings of Alavattam and Norris, would have had no reasonable expectation of success in arriving at the claimed invention of independent claims 1 and 20.

The Patent Office also states that one of ordinary skill in the art would have been motivated to form a polymeric particle utilizing poly(D,L-lactic acid-co-glycolic acid)) (such as those described in Alavattam) for encapsulating biodegradable biologically active agents utilizing the surfactants taught in Quay as surface-altering agents that would enhance transport of the particles in mucus. Applicant respectfully disagrees.

While Quay teaches a variety of mechanisms to improve the transport characteristics of biologically active agents such as proteins across hydrophobic mucosal membrane barriers, there is no teaching, suggestion or motivation in Quay that the same methods for transporting biologically active agents alone would work for biologically active agents that are associated with a particle, such that the average rate at which the particle moves in mucus would be enhanced by at least five-fold. Therefore, the results of the modifications asserted in the Office Action would not be predictable from Quay, or the combination of Alavattam, Norris, and Quay, and thus the proposed combination does not render the instant claims obvious.

If the Patent Office reconsiders the instant claims as a whole, it should be evident that there is no teaching or suggestion in Quay to provide a polymeric particle comprising a pharmaceutically acceptable polymer core, a bioactive agent, and a surface-altering agent disposed on the surface of a core that enhances the average rate at which the particles or a fraction of the particles move in mucus by at least five-fold. There is simply no teaching, suggestion or motivation in Quay to modify the conjugates discussed therein to provide polymeric particles. Similarly, there is no teaching, suggestion or motivation in Alavattam to provide particles that have increased transport in

mucus. Therefore, Quay, or the combination of Alavattam and Quay, does not render the instant claims obvious.

For example, page 7 of the Office Action points to the teachings in Quay that surface-active agents can be incorporated within mucosal delivery formulations, and that these classes of surface-active agents typically include solubilization of the biologically active agent. While these surface-active agents may allow increased transport of biologically active agents by solubilizing them to prevent aggregation of the biologically active agents, Quay does not teach or suggest that these biologically active agents and surface-active agents could be used with a polymeric particle. Furthermore, the skilled worker at the time of filing would not have been able to predict whether the mechanism of action that increases the rate of transport of the biologically active agent in mucus (e.g., by preventing aggregation of the biologically active agent) would apply when both the biologically active agent and surface-active agent are associated with a polymeric particle as claimed. Thus, the combination of the teachings in Quay with the particles disclosed in Alavattam would not lead to a reasonable expectation of success.

The Examiner on page 7 of the Office Action also points to the teachings in Quay that surfactants can be used to improve the transport characteristics of selected biologically active agents by surface charge modification (e.g., by cationization) of biologically active agents. Quay does not teach or suggest that these surface charge-modified biologically active agents could be combined with polymeric particles. Moreover, one of skill in the art at the time of filing could not have predicted that this mechanism for increasing the rate of transport of biologically active agents would be effective when the biologically active agent is associated with a polymeric particle as claimed, since the particle would be substantially larger than the biologically active agent alone as taught in Quay. Thus, the combination of the teachings in Quay with the particles disclosed in Alavattam would not lead to a reasonable expectation of success.

The Examiner on page 8 of the Office Action also points to the teachings in Quay that a bioadhesive within certain compositions can yield a two- to five-fold, often a five- to ten-fold, increase in permeability for peptides and proteins into or through the mucosal epithelium. Quay teaches that these compositions are often in the form of adhesives that have the biologically active agent mixed in to effectuate slow release or local delivery of the active agent (e.g., see paragraph

[0236]). While these compositions may allow the biologically active agent to penetrate the mucosal epithelium, Quay gives no indication of whether or not these compositions would increase the rate of transport of the biologically active agents within polymeric particles, such that the polymeric particles with a biologically active agent would be transported with these increased rates in mucus. Furthermore, Quay's teaching of the use of mucolytics and other mucolytic agents that may be incorporated with the compositions, e.g., to "degrade, thin or clear mucus" to facilitate absorption of administered biotherapeutic agents (see paragraphs [0153-0156]), may suggest that these compositions themselves do not have the intrinsic properties of increased transport in mucus. Thus, the skilled worker at the time of filing would not have been motivated to combine the teachings of Quay and Alavattam to arrive at the claimed particles. Even if the skilled worker did combine the cited documents, the combination of the teachings in Quay with the particles disclosed in Alavattam would not lead to a reasonable expectation of success.

The Examiner on page 8 of the Office Action also points to the teaching in Quay that the bioavailability of 9-desglycinamide was 3-5-fold increased compared to an aqueous solution of the peptide drug without this polymer. Applicant does not see how an increase in bioavailability of a small molecule would teach or suggest an increase in a rate of transport of a polymeric particle in mucus as claimed.

The Patent Office also points to Quay's use of mucoadhesive polymers to yield enhanced permeation effects. As the name suggests, "mucoadhesive" polymers adhere to mucus. Applicant does not see how the combination of such polymers with the bioactive small molecule agents disclosed in Quay would lead one of ordinary skill in the art to expect that such mucus adhering polymers would increase the transport of polymeric particles in mucus as claimed.

In summary, the skilled worker at the time of filing would not have been motivated to combine the teachings of Alavattam, Norris and Quay to arrive at the polymeric particles of the instant claims. The Patent Office's suggestion that it would have been obvious to combine Alavattam, Norris and Quay appears to be premised on hindsight based on the instant specification, which is not a substitute for some teaching or suggestion supporting an obviousness rejection (Schering Corp. v. Geneva Pharms, Inc., 339F.3d 1375, 1377 (Fed. Cir. 2003)). Moreover, even if

the skilled worker did combine the cited documents, the skilled worker at the time of filing would have had no reasonable expectation of success in arriving at particles of the instant claims.

For at least these reasons, the asserted combination of Alavattam in view of Norris and Quay does not render independent claims 1 and 20 obvious. The remaining claims rejected on this ground depend directly or indirectly from either claim 1 or 20, and, therefore, are also patentable over the asserted combination of Alavattam in view of Norris and Quay for at least these same reasons.

Claims 1 and 12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Alavattam, in view of Norris and Quay, and further in view of Singh et al, PNAS, 97(2): 811-816, 2000 (hereinafter, "Singh").

As described above, the asserted combination of Alavattam in view of Norris and Quay does not render claim 1 obvious. Singh also does not cure the deficiencies in the combination of Alavattam in view of Norris and Quay. Therefore, claim 1, and claim 12 which depends therefrom, is patentable in view of the asserted combination of Alavattam in view of Norris and Quay and further in view of Singh.

Claims 1 and 22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Alavattam, in view of Norris and Quay, and further in view of U.S. Patent No. 5,612,053 (hereinafter, "Baichwal").

As described above, the asserted combination of Alavattam in view of Norris and Quay does not render claim 1 obvious. Baichwal also does not cure the deficiencies in the combination of Alavattam in view of Norris and Quay. Therefore, claim 1, and claim 12 which depends therefrom, is patentable in view of the asserted combination of Alavattam in view of Norris and Quay and further in view of Baichwal.

Claims 1 and 28-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Alavattam, in view of Norris and Quay, and further in view of Dawson et al., Vet. Rec. 127(13):338, 1990 (hereinafter "Dawson").

As described above, the asserted combination of Alavattam in view of Norris and Quay does not render claims 1 or 20 obvious. Dawson also does not cure the deficiencies in the combination of Alavattam in view of Norris and Quay. Therefore, claims 1 and 20, and dependent claims 28 and

29, are patentable in view of the asserted combination of Alavattam in view of Norris and Quay and further in view of Dawson.

Accordingly, withdrawal of the claim rejections on these grounds is respectfully requested.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants believe we have appropriately provided for fees due with this response. However, if there are any other fees due in connection with filing this submission, please charge our Deposit Account No. 18-1945, under Order No. JHUC-P01-021 from which the undersigned is authorized to draw.

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